Mild, efficient cleavage of arenesulfonamides by magnesium reduction

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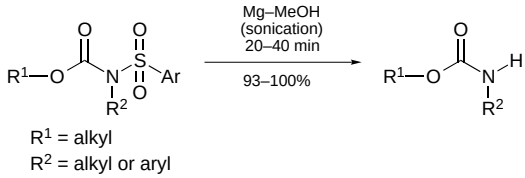
The cleavage of arenesulfonamides *via* *N*-arenesulfonylcarbamates is achieved within a few minutes under ultrasonic conditions by reaction with magnesium in anhydrous methanol.

For a long time, aromatic sulfonic acids have been used in the derivatization of amines and the protection of amino functions[1] and the resultant, generally crystalline sulfonamides are very resistant to nucleophilic attack. In addition, sulfonamides derived from primary amines can be readily deprotonated and the anions can serve as nucleophiles in reactions with alkylating reagents.[2] For the cleavage of the prototype *N*-tosyl group, reagents like sodium in liquid ammonia,[3] refluxing strong acid such as HBr in the presence of phenol[3] and sodium naphthalenide have been applied.[4] The need for such drastic conditions in the deprotection step restricted the use of tosyl and similar protecting groups to only very stable molecules and excluded the simultaneous application of many other protecting groups currently used. However, the scope widened with the development of new deprotection methods which included SmI_2,[5] Bu_3SnH–AIBN[6] and electrolysis.[7a] In the meantime, efforts were made to modify the tosyl group to make it more labile to acid. As a result, a new generation of arenesulfonyl protecting groups have emerged, *e.g.* 4-methoxybenzenesulfonyl (Mbs),[8] and the 2,2,5,7,8-pentamethylchromane-6-sulfonyl[9] and heteroarene-2-sulfonyl groups.[5b–d]



In continuation of our work dealing with the cathodic cleavage of substituted benzenesulfonamides and the corresponding *tert*-butyl sulfonylcarbamates,[7a] we now report a fast and simple method for the deprotection of substituted phenylsulfonylcarbamates using magnesium† in methanol as the cleaving agent under ultrasonic conditions. Although this system has been used previously for the cleavage of primary and secondary alkyl phenyl sulfones,[10,11] only one example dealing with the cleavage of a tosyl group attached to an indole nitrogen with magnesium turnings has been briefly reported.[12]

The *tert*-butyl *N*-arylsulfonylcarbamates and *N*-acylsulfonamides used as starting material in this work were prepared according to the procedures previously described.[7] In general primary amino functions of alkylamines and amino acids were first converted to the corresponding sulfonamides which in turn afforded alkyl arylsulfonylcarbamates almost quantitatively after treatment with Boc_2O under DMAP catalysis.

Initial cleavage experiments were carried out using 20 equiv. of magnesium in methanol at room temperature with stirring. Long reaction times (6–24 h) were thereby required to attain the

Table 1 Cleavage experiments with magnesium in methanol

Entry	Substrate	Equiv. of Mg	*t*/min	Product[a]	Yield (%)
1	Boc-N(Ph)-Ts	5	20	Boc-NHPh	99
2	Boc-N(Bn)-SO_2Ph	5	20	Boc-NHBn	99
3	Boc-N(Bn)-Ts	5	20	Boc-NHBn	99
4	Boc-N(Bn)-$SO_2C_6H_4$Br-4	5	20	Boc-NHBn	98
5	Boc-N(Bn)-Cbs[b]	5	40	Boc-NHBn	100
6	Boc-N(Bn)-$SO_2C_6H_4NO_2$-4	5	80	not isolated	
7	Boc-N(Bn)-Mbs	15	20	Boc-NHBn	100
8	Boc-N(Bn)-$SO_2C_6H_2Me_3$-2,4,6	10	25	Boc-NHBn	95
9	Boc-N(Bn)-$SO_2C_6H_2Pr^i_3$-2,4,6	10	25	Boc-NHBn	97
10	Boc(Ts)-D-Ala-OEt	5	60	Boc-D-Ala-OMe	97
11	Z(Ts)-D-Ala-OEt	5	40	Z-D-Ala-OMe	98
12	Boc(Cbs)-L-Ala-OBn	5	35	Boc-L-Ala-OMe	100
13	Boc(Ts)N[CH_2]$_2$-NHZ[c]	6	20	Boc-NH[CH_2]$_2$-NHZ	99
14	Boc(Ts)N[CH_2]$_2$-NHTroc[c]	5	40	Boc-NH[CH_2]$_2$NHDoc	87
15	Boc(Ts)N-N(Bn)Z[c]	10	35	Boc-NH-N(Bn)Z	100
16	Boc(Cbs)N-N(Bn)Z	10	35	Boc-NH-N(Bn)Z	n.d.[d]
17	Ac-N(Bn)-Ts	10	40	Ac-NHBn	81
18	Bz-N(Bn)-Ts	10	40	mixture	—
19	Ts-Indole	5	20	indole	100

[a] Products were identical with reference substances by TLC, ^{1}H NMR and/or melting point. [b] Typical experimental procedure: to a solution of substrate (186 mg, 0.5 mmol) in MeOH (6 cm^3) was added Mg powder (61 mg, 2.5 mmol, 5 equiv.). The resulting suspension was sonicated for 20 min, when TLC on silica (diethyl ether–light petroleum, 1 : 2) indicated that all starting material had been consumed. The reaction was diluted with dichloromethane (15 cm^3) and poured into 0.5 M HCl. The organic phase was washed twice with 1 M $NaHCO_3$ and brine and then dried ($MgSO_4$). Filtering through a short silica column and crystallization gave 103 mg (100%) of white crystalline product, identical with Boc-NHBn. For substrates not readily soluble in MeOH, THF can be added. A mixture of MeOH–THF 3 : 1 worked as well as neat MeOH. [c] New compound (L. Grehn, B. Nyasse and U. Ragnarsson, manuscript in preparation). [d] n.d. = not determined.

complete deprotection of $PhSO_2$, 4-cyanophenylsulfonyl (Cbs), 4-$BrC_6H_4SO_2$ and Ts groups of the corresponding *tert*-butyl arylsulfonylcarbamates, but Mbs did not cleave completely even after 24 h. When the same amount of magnesium was used and the reactions were allowed to proceed under ultrasonic conditions‡ very fast and clean cleavage took place even with Mbs-protected and sterically hindered substrates. Reactions were subsequently optimised with the *tert*-butyl *N*-benzyl derivatives in each case under sonication with the results that (i) 5 equiv. of magnesium powder were sufficient for an efficient deprotection of the $PhSO_2$, 4-$BrC_6H_4SO_2$, Cbs and Ts groups and (ii) 10 equiv. for the 2,4,6-$Me_3C_6H_2SO_2$ and 2,4,6-$Pr^i_3C_6H_2SO_2$ groups, whereas (iii) at least 15 equiv. were required for the cleavage of the Mbs-carbamate. These findings were subsequently applied in the preparative cleavage experiments involving derivatives of alanine, ethylenediamine, hydrazine and *N*-acyl sulfonamides listed in Table 1.

It should be noted that during the experiment involving the 4-$NO_2C_6H_4SO_2$ group (entry 6), a yellow mixture was obtained, probably resulting from reduction of the nitro group. The Troc containing sulfonylcarbamate (entry 14), although cleaved completely, underwent a known alkyl halide reduction mediated by the reagent,[13] giving rise to the 2,2-dichloroethoxycarbonyl (Doc) derivative. Furthermore, transesterification took place (entries 10 and 11) as previously observed during the reduction of an α,β-unsaturated ethyl ester.[14] Concerning the *N*-Ac and *N*-Bz sulfonamides (entries 17 and 18), it is worth mentioning that the cleavage of the tosyl group proceeded more selectively in the former case.

In summary, since arenesulfonamides derived from primary amines are easily converted to *tert*-butyl and similar sulfonylcarbamates by DMAP-catalysed acylation,[7] this reductive cleavage completes a two-step procedure from sulfonamides to carbamates. Furthermore, since the required sulfonylcarbamates can also be directly obtained from alcohols by the Mitsunobu reaction,[2] such carbamates can now also be made more conveniently by the present procedure.

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Footnotes

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† Magnesium powder (Merck 105815, particle size 0.06–0.3 mm) was used. The quality of methanol is critical for these experiments: we found that after addition of 0.5% of water, no reaction took place. For other applications of Mg–MeOH, see *Encyclopedia of Reagents for Organic Synthesis*, ed. L. A. Paquette, Wiley, Chichester, 1995, vol. 5, pp. 3202–3204.

‡ 35 kHz, 120–240 W (Bandelin, Berlin, type RK106).

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